Paracrine and synaptic mechanisms underlying neural stem cell-mediated stroke recovery

Grant Award Details

Paracrine and synaptic mechanisms underlying neural stem cell-mediated stroke recovery

Grant Type: Basic Biology V

Grant Number: RB5-07363

Project Objective: The original objective of this project was to was to determine if transplanted human neural stem cells (hNSCs) induce recovery after stroke by altering brain plasticity at the synaptic level, and to determine whether hNSCs altered synapse activity through paracrine effects or by direct integration into the circuitry. Unfortunately the lab discovered that the transplanted cells do not persist significantly beyond 1-week post-transplantation. Despite a lack of cell persistence, there is a durable clinical effect.
The newly approved aims included in the PAR address the objective of ultimately determining whether the effects of hNSCs on plasticity and inflammation are two separate mechanisms by which hNSCs induce recovery, or whether the changes in inflammation actually drive the plasticity changes.

Investigator:

Name:	Gary Steinberg
Institution:	Stanford University
Type:	PI

Disease Focus: Neurological Disorders, Stroke

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,178,370

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

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Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Paracrine and synaptic mechanisms underlying neural stem cell-mediated stroke recovery

Public Abstract: Stem cell therapy holds promise for the almost million Americans yearly who suffer a stroke. Preclinical data have shown that human neural stem cells (hNSCs) aid recovery after stroke, resulting in a major effort to advance stem cell therapy to the clinic, and we are currently transitioning our hNSC product to the clinic for stroke therapy. In this proposal we will explore how these cells improve lost function. We have already shown that injected hNSCs secrete factors that promote the gross rewiring of the brain, a major component of the spontaneous recovery observed after stroke. We now intend to focus on the connections between neurons, the synapses, which are a critical part of this rewiring process. We aim to quantify the effect of hNSCs on synapse density and function, and explore whether the stem cells secrete restorative synaptogenic factors or form functional synapses with pre-existing neurons. Our pursuit is made possible by our combination of state-of-the-art imaging techniques enabling us to visualize, characterize, and quantify these tiny synaptic structures and their interaction with the hNSCs. Furthermore, by engineering the hNSCs we can identify the factors they secrete in the brain and identify those which modulate synaptic connections. Our proposed studies will provide important insight into how transplanted stem cells induce recovery after stroke, with potential applicability to other brain diseases.

Statement of Benefit to California: Cerebrovascular stroke is the fourth leading cause of mortality in the United States and a significant source of long-term physical and cognitive disability that has devastating consequences to patients and their families. In California alone, over 9% of adults 65 years or older have had a stroke according to a 2005 study. In the next 20 years the societal toll is projected to amount to millions of patients and 18.8 billion dollars per year in direct medical costs. To date, there is no approved therapeutic agent for the recovery phase after stroke, making the long-term care of stroke patients a tremendous socioeconomic burden that will continue to rise as our aging population increases. Our laboratory and others have demonstrated the promise of stem cell transplantation to treat stroke. We are dedicated to developing human neural stem cells (hNSCs) as a novel neuro-restorative treatment for lost motor function after stroke. The goal of our proposed work is to further understand how transplanted hNSCs improve stroke recovery, as dissecting the mechanism of action of stem cells in the stroke brain will ultimately improve the chance of clinical success. This could potentially provide significant cost savings to California, but more importantly benefit the thousands of Californians and their families who struggle with the aftermath of stroke.